

What is claimed is:

1. A method comprising the steps of: (a) providing a sample suspension containing at least one set of G protein beads, each of said G-protein beads comprising epitope-recognizing beads having a heterotrimeric G protein bound thereto; (b) mixing said sample suspension with at least one type of G protein coupled receptor and a ligand to thereby form a mixed suspension containing a ligand-receptor-G protein complex when said G protein is capable of forming a complex with said receptor and said ligand; (c) mixing said mixed suspension to incubate said mixed suspension and thereby form an incubated suspension; (d) detecting the formation of a stable ligand-receptor-G protein complexes on the said beads in said incubated suspension by flow cytometry.
2. The method of claim 1, further comprising the step of determining whether said G protein is capable of forming a complex with said receptor and said ligand, wherein said receptor and said ligand are known to form a complex with an unknown G protein.
3. The method of claim 1, further comprising the step of determining whether said ligand is capable of forming a complex with said G protein and said receptor, wherein said G protein and said receptor are known to form a complex with another ligand.
4. The method of claim 1, further comprising forming said G protein beads by binding epitope-bearing G protein subunits to epitope-recognizing beads.
5. The method of claim 1, wherein said epitope-recognizing beads comprise beads that recognize the FLAG epitope.
6. The method of claim 1, wherein said epitope-recognizing beads comprise beads that recognize the six-histidine (H6) epitope.
7. The method of claim 1, further comprising the step of solubilizing said receptor.

8. The method of claim 1, wherein said epitope-recognizing beads are derivatized to carry chelated nickel.
9. The method of claim 1, wherein the beads displaying said heterotrimeric G protein include a fluorescent address tag.
10. The method of claim 1, wherein said ligand includes a fluorescent tag.
11. The method of claim 1, wherein said receptor is fluorescent.
12. The method of claim 11, wherein said receptor is made fluorescent by chemical derivatization of said receptor.
13. The method of claim 11, wherein said receptor is made fluorescent by making a fusion protein of said receptor with a fluorescent protein.
14. The method of claim 1, wherein said at least one set of G protein beads comprises at least two sets of G protein beads, each of said sets of G protein beads having a different respective fluorescent color and a different respective heterotrimeric G protein bound thereto; wherein all of said sets of G protein beads are simultaneously present in said mixed suspension; and wherein step (d) comprises detecting the respective fluorescent color associated with each set of G protein beads separately.
15. The method of claim 14, wherein said at least one type of G protein coupled receptor comprises at least two types of G protein coupled receptors.
16. The method of claim 1, wherein said at least one type of G protein coupled receptor comprises at least two types of G protein coupled receptors, each of said types of G protein coupled receptors having a different fluorescent color; wherein all of said types of G protein coupled receptors are simultaneously present in said mixed suspension; and wherein step (d) comprises detecting the respective fluorescent color associated with each

of said types of G protein coupled receptors separately.

17. The method of claim 16, wherein G protein beads have a first fluorescent color, wherein said ligand is bound to ligand bearing beads having a second fluorescent color, wherein said G protein beads and said ligand bearing beads are present simultaneously in said mixed suspension, and wherein step (d) comprises detecting the respective fluorescent color associated with said G protein beads and said ligand bearing beads separately.

18. The method of claim 1, wherein a regulator of G protein signaling is mixed with said mixed suspension and wherein said method further comprises the following step: (e) determining the effect of said regulator of G protein signaling upon ternary complex formation.

19. The method of claim 18, wherein said at least one set of G protein beads comprises at least two sets of G protein beads, each of said sets of G protein beads having a different respective fluorescent color and a different respective heterotrimeric G protein bound thereto; wherein all of said sets of G protein beads are simultaneously present in said mixed suspension; wherein step (d) comprises detecting the respective fluorescent color associated with each set of G protein beads separately, and wherein step (e) comprises determining the effect of said regulator of G protein signaling upon ternary complex formation for each of said sets of G protein beads.

20. The method of claim 19, wherein said at least one type of G protein coupled receptor comprises at least two types of G protein coupled receptors and wherein step (e) comprises determining the effect of said regulator of G protein signaling upon ternary complex formation for each of said types of G protein coupled receptors.

21. The method of claim 18, wherein said at least one type of G protein coupled receptor comprises at least two types of G protein coupled receptors, each of said types of G protein coupled receptors having a different fluorescent color; wherein all of said types of

G protein coupled receptors are simultaneously present in said mixed suspension; wherein step (d) comprises detecting the respective fluorescent color associated with each of said types of G protein coupled receptors separately; and wherein step (e) comprises determining the effect of said regulator of G protein signaling upon ternary complex formation for each of said types of G protein coupled receptors.

22. A method claim 18, comprising forming said G protein beads by the steps of: providing epitope-recognizing beads; and binding epitope-bearing G protein subunits to said epitope-recognizing beads to form G protein beads.

23. The method of claim 22, wherein said epitope-recognizing beads comprise beads that recognize the FLAG epitope.

24. The method of claim 22, wherein said epitope-recognizing beads comprise beads that recognize the six-histidine (H6) epitope.

25. The method of claim 22, wherein said epitope-recognizing beads are derivatized to canny chelated nickel.

26. The method of claim 22, wherein said heterotrimeric G protein includes a fluorescent tag.

27. A method comprising evaluating a G protein coupled receptor agonism or antagonism of a compound by a bead-based flow cytometric process comprising contacting the compound with beads conjugated to a G protein coupled receptor ligand which would result in a detectable G protein coupled receptor ligand-receptor complex, to determine the existence of an interaction or an absence of an interaction with said receptor, wherein the extent to which the compound competes with said ligand-receptor complex determines that a compound is an agonist or an antagonist of said G protein coupled receptor.

28. A method comprising evaluating a  $\beta$ 2-adrenergic receptor agonism or antagonism of a compound by a bead-based flow cytometric process comprising contacting the compound with beads conjugated to a  $\beta$ 2-adrenergic receptor ligand which would result in a detectable  $\beta$ 2-adrenergic receptor ligand-receptor complex, to determine the existence of an interaction or an absence of an interaction with said receptor, wherein the extent to which the compound competes with said ligand-receptor complex determines that a compound is an agonist or an antagonist of said  $\beta$ 2-adrenergic receptor.

29. A method of claim 28, wherein the beads are dihydroalprenolol-conjugated beads.

30. A method comprising evaluating a G-protein receptor agonism or partial agonism of a compound in a bead based high throughput screening system comprising a) contacting the compound and solubilized detectable G protein coupled receptor with G protein beads, each of said G-protein beads comprising epitope-recognizing beads having an epitope-tagged heterotrimeric G protein bound thereto; and b) determining whether a ternary complex between said G protein coupled receptor and said G protein occurs, wherein an interaction between receptor and G protein evidences that said compound is an agonist or partial agonist of said G protein coupled receptor.

31. A method of claim 30, wherein the G protein receptor is the  $\beta$ 2-adrenergic receptor, said receptor contains a fluorescent moiety, and the interaction between said receptor and said G protein evidences that said compound is an agonist of said receptor.

32. A method of claim 30, wherein said the detectable moiety is a any fluorescent protein.

33. A method of claim 31, wherein the  $\beta$ 2-adrenergic receptor is a  $\beta$ 2AR-GFP fusion protein.

34. A method of claim 30, wherein detectable ternary complex levels are used to generate dose-response curves that are indicative of the compound's  $\beta$ 2-adrenergic receptor agonism or antagonism.
35. A method of claim 30, wherein GTP $\gamma$ S-induced activation rates for the detectable ternary complex are determined and wherein compounds that are  $\beta$ 2-adrenergic receptor agonists or partial  $\beta$ 2-adrenergic receptor agonists have approximately equal GTP $\gamma$ S-induced activation rates.
36. A method comprising evaluating the relative G protein receptor agonism or partial agonism a compound by a flow cytometric process comprising contacting the compound and soluble detectable G protein receptor with beads conjugated to epitope-recognizing beads having a heterotrimeric G protein bound thereto, wherein an agonist or partial agonist compound binds to G protein receptor to form a compound-receptor complex and said compound-receptor complex binds to said bound G protein to form a detectable ternary complex indicative of the compound's G protein receptor agonism or antagonism.
37. A method of claim 36, wherein the G protein receptor is a  $\beta$ 2-adrenergic receptor containing a fluorescent moiety.
38. A method of claim 37, wherein the fluorescent moiety is a GFP or a RFP fused to said G protein receptor.
39. A method of claim 36, wherein the detectable  $\beta$ 2-adrenergic receptor is a  $\beta$ 2AR-GFP fusion protein.
40. A method of claim 36, wherein GTP $\gamma$ S-induced activation rates for the detectable ternary complex are determined and wherein compounds that are  $\beta$ 2-adrenergic receptor agonists or partial  $\beta$ 2-adrenergic receptor agonists have approximately equal GTP $\gamma$ S-induced activation rates.

41. A method of evaluating a library of compounds comprising:  
selecting a plurality of compounds from the library;  
evaluating the relative  $\beta$ 2-adrenergic receptor agonism of each selected compound by a flow cytometric process comprising contacting the compound with beads conjugated to a  $\beta$ 2-adrenergic receptor-detectable moiety complex, wherein the extent to which the compound complexes with the  $\beta$ 2-adrenergic receptor-detectable moiety complex to form a detectable ternary complex is determined by measuring detectable ternary complex levels and detectable ternary complex levels are indicative of the compound's  $\beta$ 2-adrenergic receptor agonism or antagonism; and  
evaluating a differentiation state or a metabolic parameter of the cell or organism.

42. A method comprising evaluating the relative G protein receptor agonism, antagonism or inactivity of a compound for a G protein coupled receptor (GPCR) in a single sample by a flow cytometric process comprising the steps of (a) providing a sample suspension containing a detectable GPCR, a set of G protein beads which will form a ternary complex with said detectable GPCR in the presence of an agonist or partial agonist, and a set of ligand beads which will bind to said detectable GPCR, said set of G-protein beads comprising epitope-recognizing beads having a heterotrimeric G protein bound thereto; (b) mixing said sample suspension with said compound; and (c) detecting the formation or absence of formation of a complex between said compound and said detectable GPCR, wherein a GPCR antagonist prevents binding of said detectable GPCR to said G protein beads by preventing ternary complex formation and prevents binding of said detectable GPCR to said ligand bead; a GPCR agonist allows binding of said detectable GPCR to said G protein beads by forming a ternary complex but prevents binding of said detectable GPCR to said ligand bead; and an inactive compound prevents binding of said detectable GPCR to said G protein beads by not promoting ternary complex formation but allows binding of said detectable GPCR to said ligand bead.

43. A method of claim 42, wherein the G protein coupled receptor is a  $\beta$ 2-adrenergic receptor containing a fluorescent moiety.

44. A method of claim 42, wherein the fluorescent moiety is any fluorescent protein fused to said G protein coupled receptor.
45. A method of claim 43, wherein the detectable  $\beta$ 2-adrenergic receptor is a  $\beta$ 2AR-GFP fusion protein.
46. The method of claim 42 wherein said G protein beads are modified with a fluorescent moiety.
47. The method of claim 46 wherein said fluorescent moiety is Texas Red.
48. A method comprising identifying agents useful in the treatment of a disease associated with G protein coupled receptor (GPCR) agonism or antagonism by determining an agent's GPCR agonism or antagonism by a flow cytometric process comprising: (a) providing a sample suspension containing a detectable GPCR, a set of G protein beads which will form a ternary complex with said detectable GPCR in the presence of an agonist or partial agonist, and a set of ligand beads which will bind to said detectable GPCR, said set of G-protein beads comprising epitope-recognizing beads having a heterotrimeric G protein bound thereto; (b) mixing said sample suspension with said agent; and (c) detecting the formation or absence of formation of a complex between said agent and said detectable GPCR, wherein a GPCR antagonist prevents binding of said detectable GPCR to said G protein beads by not promoting ternary complex formation and prevents binding of said GPCR to said ligand bead; and a GPCR agonist allows binding of said detectable GPCR to said G protein beads by forming a ternary complex but prevents binding of said detectable GPCR to said ligand bead.
49. A method of claim 48, wherein the G protein receptor is a  $\beta$ 2-adrenergic receptor containing a fluorescent moiety.
50. A method of claim 48, wherein the fluorescent moiety is any fluorescent protein fused to said G protein receptor.



51. A method of claim 49, wherein the detectable  $\beta$ 2-adrenergic receptor is a  $\beta$ 2AR-GFP fusion protein.
52. The method of claim 48 wherein said G protein beads are modified with a fluorescent moiety.
53. The method of claim 46 wherein said fluorescent moiety is Texas Red.
54. A method comprising evaluating a G protein coupled receptor agonism or antagonism of a compound by a bead-based flow cytometric process comprising contacting the compound with beads conjugated to a ligand which would result in a detectable G protein coupled receptor ligand-receptor complex, to determine the existence of an interaction or an absence of an interaction with said detectable receptor, and comparing said interaction with said ligand-receptor complex with a ligand-receptor complex utilizing a known agonist or antagonist to determine that a compound is an agonist or an antagonist of said G protein coupled receptor.
55. A method of evaluating a library of compounds comprising:  
selecting a plurality of compounds from the library;  
evaluating the relative  $\beta$ 2-adrenergic receptor agonism or antagonism of each selected compound by a flow cytometric process comprising contacting the compound with beads conjugated to a ligand for a  $\beta$ 2-adrenergic receptor-detectable moiety complex, wherein the extent to which the compound complexes with the  $\beta$ 2-adrenergic receptor-detectable moiety and binds to said ligand conjugated beads is indicative of agonist or antagonist activity; and  
evaluating a differentiation state or a metabolic parameter of the cell or organism.